

Carcinosarcoma of ovary, its histopathological, management and prognostic analysis with review of literature

Abstract

Carcinosarcoma is a mixed malignant biphasic tumour with rare entity and comprises of both epithelial and mesenchymatous components. Primary ovarian carcinosarcoma is a rare neoplasm with number of cases reported in the literature in hundreds and accounts for less than 1% of all ovarian tumours. These tumours are usually diagnosed at an older age and at an advanced stage. It has aggressive clinical behaviour and survival depends on stage at presentation. Radiological imaging findings cannot differentiate carcinosarcomas from other ovarian cancers. Diagnosis is based upon histological findings. Cytoreductive debulking surgery is a crucial part in the treatment of carcinosarcoma of ovary. The role of adjuvant chemotherapy regimen is still controversial. Combination chemotherapy with taxane and platinum based regimen or ifosfamide and platinum based regimen are considered as adjuvant treatment. Despite aggressive treatment modalities such as surgery and chemotherapy, there is poor outcome. Response to therapy and overall survival are poor in comparison to epithelial ovarian malignancies. But due to rarity of the disease, such poor prognosis needs collaboration of studies with molecular analysis to obtain new therapeutic guidelines to improve survival of the patients.

Keywords: Carcinosarcoma, chemotherapy, cytoreductive surgery, heterologous elements, prognosis, ovary.

Introduction

Ovarian cancer is the second most common gynaecologic cancer and is one of the most lethal female malignancies [1]. Sarcomas are rare malignancies of ovary. Carcinosarcoma, leiomyosarcoma, rhabdomyosarcoma, fibromyosarcomas and angiomyosarcomas are the possible different type of sarcomas in ovary [2]. Carcinosarcoma is the most frequent subgroup among these. Ovarian carcinosarcoma is a rare subtype of ovarian cancer with an aggressive behaviour and poor prognosis. Survival of ovarian carcinosarcoma in both early and late stage is inferior to serous ovarian carcinomas [3]. In female genital tract it is commonly seen in uterus and ovarian pathology is a rare entity. Peritoneal, fallopian tubes, cervical and vaginal carcinosarcoma are also rarely seen [4]. Ovarian carcinosarcoma is also known as malignant mixed mullerian tumours (MMMT). Majorities occur in postmenopausal women and only 10% of cases occur only in younger women [5]. There are no standard guidelines for the treatment. The data published in the literature are only retrospective reviews and few institutions are able to do prospective studies. According to some studies,

optimal cytoreductive surgery followed by adjuvant chemotherapy may be associate with improved survival [6,7-9]. The purpose of the review is to compare and give a extensive idea from the published data regarding management and prognosis of the disease.

41
42

43

44 **Incidence**

Ovarian cancer is the fifth leading cause of cancer related death among women and 22,280 cases with 15,500 deaths reported in 2012 [10]. Majorities are epithelial types with serous subtype being the most common. Carcinosarcoma is a rare histological subtype of ovarian malignancy and is diagnosed in 1-4% among all ovarian cancer survivors [11,12-15,16]. Carcinosarcoma of the ovary is nearly three times less prevalent than that of uterus [17]. Majorities are seen in Caucasian and present at advanced stages [6]. Fewer than 400 cases have been reported in the literature [14]. The mean age of presentation is 65 years [14]. Pelvic irradiation may increase the incidence of MMMT [18].

53

54 **Histogenesis**

55

A recent study shows a monoclonal theory of histogenesis in ovarian carcinosarcomas. According to this, metaplastic transformation of the epithelial component causes tumourigenesis resulting in formation of sarcomatous component [19]. But, high rate of recurrence in MMMT of ovary treated with platinum based regimen suggesting insufficiency of the theory. Further study on molecular characteristics is necessary to develop knowledge regarding specific targeted therapies to increase survival outcome.

62

Three theories try to explain the histogenesis of MMMTs [5]:

- 64 - Combination theory: It suggests that both cellular lines come from the same stem
65 cell.
- 66 - Collision theory: It proposes that two different cellular lines with different mutations
67 generate the tumour.
- 68 - Conversion theory: It suggests that a cellular line already carrying the mutation
69 suffers a metaplastic transformation, producing a further cellular clone.

70

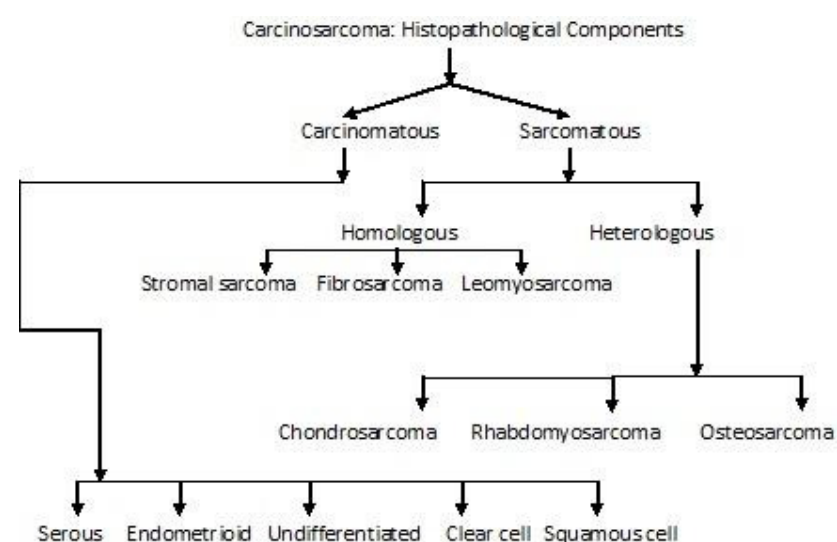
71 **Histopathology**

72

Histopathologically, it is composed of both carcinomatous and mesenchymal components. Sarcomatous component can be homologous (composed of tissues that normally found in ovary) or heterologous (composed of tissues not normally found in ovary) basing on origin of its mesenchymal tissue [20]. Homogenous part may be endometrial stromal sarcoma, fibrosarcoma, and leomyosarcoma. Heterogenous part may be chondrosarcoma, rhabdomyosarcoma, and osteosarcoma [21]. Carcinomatous components can be serous,

endometrioid, undifferentiated carcinoma, clear cell carcinoma or squamous cell carcinoma [12,18,22]. Epithelial component mostly present in multiple forms and serous components are more common than endometrioid components with an inferior prognosis [23]. Clear cell and squamous cell components are rarely seen. In majority cases epithelial components are responsible for tumour progression and distant metastases [24]. Homologous sarcomatous component do not carry a better prognosis than heterologous sarcomatous components [23,25-27]. Histopathological components in carcinosarcoma of ovary are described in figure-1 in schematic form.

Figure-1:



According to Boucher et al., equal representation of the epithelial endometrioid and serous component types in ovarian carcinosarcomas and mesenchymal component is largely heterologous, of chondromatous and rhabdomyoblastic differentiation [20]. According to Kunkel et al., serous carcinomatous components overwhelms and also a predominance of heterologous chondromatous components [28]. Menon et al found endometrioid carcinoma and heterologous rhabdomyosarcoma as predominant components [19]. According to Patnayak et al., serous carcinoma as predominant epithelial component and rhabdomyosarcoma as predominant sarcomatous component [30].

Due to lack of standardized data on histopathological analysis, the predominant epithelial and mesenchymal components with their prognosis is still controversy and needs detail analysis at molecular level with large data for evaluation and to draw a conclusion.

103 Table-1: showing predominant epithelial and mesenchymal components in carcinosarcoma
104 of ovary

Literature	Predominant Carcinomatous component	Predominant Sarcomatous component
Boucher et al (1994)	Endometrioid = serous	Heterologous (chondromatous and rhabdomyoblastic)
Kunkel et al (2012)	Serous component	Heterologous chondromatous
Menon et al (2013)	Endometrioid component	Heterologous rhabdomyosarcomatous component
Patnayak et al (2010)	Serous	Heterologous rhabdomyosarcomatous component

105

106 Immunohistochemical examination is used for confirmation of diagnosis. Cytokeratin and
107 epithelial membrane antigen are positive for epithelial component. Vimentin, smooth
108 muscle actin, CD10, desmin, and myoglobine are positive in mesenchymal components.
109 S100 is used to detect chondroid or adipose tissue differentiation [5].

110 **Clinical diagnosis**

111 Clinical features:

112 Ovarian carcinosarcoma follows a distinct natural history compared to other epithelial
113 ovarian carcinomas [5,12,15], tend to occur in older women with more often presents at
114 disseminated disease and with inferior prognosis. Majoritis have predilection for early
115 dissemination [5,7,12,15,16]. The way of clinical presentation is similar to epithelial ovarian
116 malignancy. Abdominal distension and pain, nausea, vomiting and weight loss are common
117 symptomatic findings. On clinical examination, palpable mass and ascitis are common
118 findings. Presence of epithelial and mesenchymal components behaves in independent
119 manner particularly in metastatic patterns. Transperitoneal spread is exclusively occur by
120 epithelial component and rarely occur by sarcomatous component [30]. Metastases usually
121 involves serosal and peritoneal seeding. A recent study showing elevated liver parenchymal
122 metastases in comparison to classical epithelial ovarian carcinoma; the pelvic recurrence,
123 liver metastases and peritoneal metastases are 31%, 23% and 19% respectively [31].

124 Serum markers:

125 Tumour marker CA125 is elevated in 74% of patients. AFP marker is rarely elevated [32]. In
126 a study by Menon et al., preoperative CA125 is raised in in 9 out of 12 cases of ovarian
127 carcinosarcoma and ascetic fluid cytology analysis revealed adenocarcinomatous deposits
128 [19]. In a case report by Patnayak et al, CA125 is elevated [29].

129 Imaging studies:

Ultrasonography is the initial radiological investigation of choice. Ultrasonographically tumours are large, composed of solid, cystic or mixed components with thick septa. MRI of abdomen describes the better characteristics of the tumour.

Staging classification system is similar to FIGO system applied to the other ovarian carcinosarcomas [33].

Preoperative diagnosis of the primary ovarian carcinosarcoma remains a challenging situation. Both the clinical and radiological findings are not specific for ovarian carcinosarcoma and are similar to other ovarian malignancies [34]. There is no specific serum marker for ovarian carcinosarcoma and also cytological analysis of ascetic fluid may not give relevant components for carcinosarcoma. The definite diagnosis of carcinosarcoma can only possible by histopathological examination of the resected specimen.

Treatment

Standard treatment consists of bilateral salpingo-oophrectomy, total abdominal hysterectomy, debulking of peritoneal metastases, and lymphadenectomy [16,17,23]. Treatment of ovarian carcinosarcoma is based upon FIGO staging. In stage I, total hysterectomy plus bilateral salpingo-oophorectomy, omentectomy, lymphadenectomy, and removal of any suspicious mass should be performed. In other stages, cytoreductive surgery should be performed like in other ovarian malignancies. The role of cytoreductive surgery is well established in epithelial ovarian carcinoma; but in carcinosarcoma it is still doubtful due to insufficient data. Recently Gynaecological oncology group (GOG) reported platinum as first line treatment with good response [33]. The role of radiation therapy is not still established [33].

Till date there is no consensus regarding optimal adjuvant chemotherapy regimens in ovarian carcinosarcoma. Many chemotherapeutic regimens already used in different centres without any standard conclusions. Women with ovarian carcinosarcoma have relatively less response to chemotherapy than epithelial ovarian cancers [16]. According to GOG, poor response rate and high toxicity with doxorubicin for ovarian carcinosarcoma. Most chemotherapeutic regimens are simplified into platinum containing regimens versus non-platinum containing regimens. Many institutions follow ifosfamide with platinum based combination regimen while others follow taxane with platinum based combination regimen. Both the ifosfamide [35] and platinum [36-38] have demonstrated efficacy in both ovarian and endometrial carcinosarcoma. Carboplatin and paclitaxel combination chemotherapy regimen has a response rate up to 72% in carcinosarcoma of the reproductive tract with more favourable toxicity profile than ifosfamide and platinum regimen [39,40,41]. Current idea regarding adjuvant chemotherapy is still unclear but with increase trend for favouring platinum-based therapy [42]. Literatures showed 68% overall response rate in the platinum containing regimens and 23% response rate in non-platinum containing regimens [40,43]. In an analysis of 22 patients, treatment with carboplatin and paclitaxel versus cisplatin and ifosfamide found no survival difference [44]. Rutledge and co-workers found improved survival in women with ovarian carcinosarcoma treated with ifosfamide combination regimen [45]. According to Chun et al, women who received paclitaxel/platinum-based combination chemotherapy had longer progression free interval and overall survival [9].

According to Paulsson et al, a retrospective series of 81 Swedish cases demonstrated that, compared to those with an incomplete regimen, the 57% of subjects who completed 6 cycles of platinum based chemotherapy had improved overall survival [48]. Combination chemotherapy regimen with cisplatin/ ifosfamide, and also paclitaxel/carboplatin have been tried in some studies with details [14,27,39,44,45,47,49].

Prognosis

MMMT is an aggressive tumour with poor survival outcome. MMMT of ovary carries more favourable prognosis than that of the uterus [17] but with worse prognosis in comparison to serous carcinoma of the ovary [16,50,51]. A case-control study with 50 women of ovarian carcinosarcoma showed 24 months of overall median survival, inferior to 41 months for women with serous carcinomas [5]. One study showed inferior survival for ovarian carcinosarcoma with advanced stage disease in comparison to that of serous carcinomas whereas no statistically significant difference in survival between these two histologic subtypes for early stage diseases [15]. In a recent study survival is inferior for all the stages of ovarian carcinosarcomas in comparison to serous carcinomas and survival was only 65% for carcinosarcomas stage I whereas 81% for those with serous carcinomas [3]. It is an aggressive subtype of epithelial cancer diagnosed at advanced stage [6,48,50,52]. The median survival is 8-16 months in MMMTs [23]. In majority studies, the median survival was nearly 18 months [17,18,25,27-29,37,48]. The age and stage are associated with overall survival [6,9,16,39,53]. Age >70 years carries worse prognosis [31]. Heterologous sarcoma component and high grade indifferntiation of the epithelial component are two poor histological prognostic factors [11]. Also, the extent of cytoreductive surgery and residual status correlate with outcome [54]. Some literature reported inferior prognosis associated with higher residual tumour burden [14,16,23,39,45,55]. According to previous data, the optimal cytoreduction means ≤ 2 centimeters diameter of residual disease remaining [52,16,39,53,40]. But recently the optimal cytoreduction means no longer than 1 centimeter in diameter of residual disease after primary surgery [56]. But, it is better if no gross residual disease after cytoreductive surgery [15]. In a retrospective study of ovarian carcinosarcoma by Rauh-Hain et al, patient with microscopic residual disease had OS of 47 months, those with macroscopic residual disease ≤ 1 cm had OS of 18 months and those with suboptimal cytoreduction had OS of 8 months [5]. Patients treated with optimal cytoreduction were with median survival of 25 months whereas it was 8 months in cases with suboptimal cytoreduction [57].

Table-2: Adverse prognostic factors

Advance age
Advance stage
Predominant epithelial tumours
Predominant serous subtype [23]
Heterologous elements [58]

Suboptimal cytoreductive surgery
Post operative higher residual disease burden
Poor response to therapy

208

209 Conclusion

210 MMT of ovary are rare tumours with aggressive behaviour, majorities present at an older
 211 age, advanced stage at the time of diagnosis and survival varies with stage of the disease
 212 and histological types. Despite all aggressive modalities of treatment there is increased risk
 213 of death with poor prognosis in comparison to epithelial ovarian carcinoma. Such rare
 214 disease with poor prognosis needs more number of prospective studies to better
 215 understand the molecular characteristics of MMT and to give idea on new therapeutic
 216 regimens to improve survival of the patients.

217 References

- 218 1. Winter WE, Maxwell GL, Tian C, et al. Prognostic factors for stage III epithelial
 219 ovarian cancer: a gynecologic oncology group study. *Journal of Clinical Oncology*
 220 2007;25(24):3621–3627.
- 221 2. Magné N, Pacaut C, Auberdiac P, Jacquin P, Chargari C, Chauleur C and Meder C.
 222 Sarcoma of vulva, vagina and ovary. *Best Pract Res Cl Ob* 2011, 25: 797-801.
- 223 3. Erin M. George, Thomas J. Herzog, Alfred I. Neugut, Yu-Shiang Lu, William M. Burke,
 224 Sharyn N. Lewin, Dawn L. Hershman, and Jason D. Wright. Carcinosarcoma of the
 225 Ovary: Natural History, Patterns of Treatment, and Outcome. *Gynecol Oncol*. 2013;
 226 131(1): 42–45.
- 227 4. Sahoo TK, Nayak R, Das SK, Dhal I, Majumdar SKD, Parida DK. carcinosarcoma of
 228 ovary and its management, a case report and review of literature. *Indian Journal of*
 229 *Medical Case Reports* 2014;3 (4):27-30.
- 230 5. Rauh-Hain JA, Growdon WB, Rodriguez N, Goodman AK, Boruta DM 2nd, Schorge JO,
 231 Horowitz NS, del Carmen MG. Carcinosarcoma of the ovary: a case-control study.
 232 *Gynecologic.Oncology*,2011; 121: 477-481.
- 233 6. Chang J, Sharpe JC, A'Hern RP, Fisher C, Blake P, Shepherd J, et al. Carcinosarcoma of
 234 the ovary: incidence, prognosis, treatment and survival of patients. *Ann Oncol*. 1995;
 235 6(8):755–8.
- 236 7. Sood AK, Sorosky JI, Gelder MS, Buller RE, Anderson B, Wilkinson EJ, et al. Primary
 237 ovarian sarcoma: analysis of prognostic variables and the role of surgical
 238 cytoreduction. *Cancer*. 1998; 82(9):1731–7.
- 239 8. Le T, Krepart GV, Lotocki RJ, Heywood MS. Malignant mixed mesodermal ovarian
 240 tumor treatment and prognosis: a 20-year experience. *Gynecologic Oncology*
 241 1997;65(2):237–240.
- 242 9. Chun KC, Kim JJ, Kim DY, et al. Optimal debulking surgery followed by
 243 paclitaxel/platinum chemotherapy is very effective in treating ovarian
 244 carcinosarcomas: a single center experience. *Gynecologic and Obstetric Investigation*
 245 2011;72(3):208–214.
- 246 10. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin*. 2012;
 247 62(1):10–29.

11. Silasi DA, Illuzzi JL, Kelly MG , Rutherford TJ, Mor G, Azodi M, Schwartz PE. Carcinosarcoma of the ovary. *Int J Gynecol Cancer* 2008; 18: 22-29.
12. del Carmen MG, Birrer M, Schorge JO. Carcinosarcoma of the ovary: a review of the literature. *Gynecol Oncol.* 2012; 125(1):271–7.
13. Mano MS, Rosa DD, Azambuja E, Ismael G, Braga S, D'Hondt V, et al. Current management of ovarian carcinosarcoma. *Int J Gynecol Cancer.* 2007; 17(2):316–24.
14. Harris MA, Delap LM, Sengupta PS, Wilkinson PM, Welch RS, Swindell R, et al. Carcinosarcoma of the ovary. *Br J Cancer.* 2003; 88(5):654–7.
15. Barnholtz-Sloan JS, Morris R, Malone JM Jr. Munkarah AR. Survival of women diagnosed with malignant, mixed mullerian tumors of the ovary (OMMMT). *Gynecol Oncol.* 2004; 93(2):506–12.
16. Brown E, Stewart M, Rye T, Al-Nafussi A, Williams AR, Bradburn M, et al. Carcinosarcoma of the ovary: 19 years of prospective data from a single center. *Cancer.* 2004; 100(10):2148–53.
17. Garg G, Shah JP, Kumar S, Bryant CS, Munkarah A, et al. Ovarian and uterine carcinosarcomas: a comparative analysis of prognostic variables and survival outcomes. *Int J Gynecol Cancer* 2010;20: 888-894.
18. Mok JE, Kim YM, Jung MH, Kim KR, Kim DY, Kim JH, Kim YT, Nam JH. Malignant mixed müllerian tumors of the ovary: experience with cytoreductive surgery and platinum-based combination chemotherapy. *Int J Gynecol Cancer* 2006; 16: 101-105.
19. Menon S, Deodhar K, Rekhi B, Dhake R, Gupta S, Ghosh J, *et al.* Clinico-pathological spectrum of primary ovarian malignant mixed mullerian tumors (OMMMT) from a tertiary cancer institute: A series of 27 cases. *Indian J Pathol Microbiol* 2013;56:365-71.
20. Boucher D, Têtu B. Morphologic prognostic factors of malignant mixed müllerian tumors of the ovary: A clinicopathologic study of 15 cases. *Int J Gynecol Pathol* 1994;13(1):22-28.
21. Cantrell LA and Van Le L. Carcinosarcoma of the ovary a review. *Obstetrical and Gynecological Survey* 2009;64:673-680.
22. Navirini R, Pineda RL. Malignant mixed mullerian tumors of the ovary. *curr opin obstet gynecol* 2006; 18:20-23.
23. Athavale R, Thomakos N, Godfrey K, Kew F, Cross P, et al. The effect of epithelial and stromal tumor components on FIGO stages III and IV ovarian carcinosarcomas treated with primary surgery and chemotherapy. *Int J Gynecol Cancer* 2007;17: 1025-1030.
24. Sreenan J, Hart W. Carcinosarcomas of the female genital tract. A pathologic study of 29 metastatic tumors: Further evidence of the dominant role of the epithelial component and the conversion theory of histogenesis. *Am J Surg Pathol* 1995;19: 666-674.
25. Barakat RR, Rubin SC, Wong G, Saigo PE, Markman M, et al. Mixed mesodermal tumor of the ovary: analysis of prognostic factors in 31 cases. *Obstet Gynecol* 1992;80: 660-664.
26. Hellström AC, Tegerstedt G, Silfverswärd C, Pettersson F. Malignant mixed müllerian tumors of the ovary: histopathologic and clinical review of 36 cases. *Int J Gynecol Cancer* 1999;9: 312-316.

27. Inthasorn P, Beale P, Dalrymple C, Carter J. Malignant mixed mullerian tumour of the ovary: prognostic factor and response of adjuvant platinum-based chemotherapy. *Aust N Z J Obstet Gynaecol* 2003;43: 61-64.
28. Kunkel J, Peng Y, Tao Y, Krigman H, Cao D. Presence of a sarcomatous component outside the ovary is an adverse prognostic factor for primary ovarian malignant mixed mesodermal/mullerian tumors: A clinicopathologic study of 47 cases. *Am J Surg Pathol* 2012;36:831-7.
29. Patnayak R, Jena A, Prakash J, Sundaram R, Vijaylaxmi B, Lakhmi AY. Primary Carcinosarcoma of Ovary an Unusual Tumor Case Report with Review of Literature. *Journal of Basic and Clinical Reproductive Sciences* 2015;4(1):39-42.
30. Reed N, Millan D, Verheijen R, Castiglione M. Nonepithelial ovarian cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21(Suppl 5): v31–v36.
31. Petru E, Haas J, Beganovic S, Kolovetsiou V, Woltsche N. Carcinosarcoma (Malignant Mixed Muellerian Tumor) of the Ovary-A Single Institution Experience of 25 years. *Int J Gynecol Clin Pract* 2015;2: 107.
32. Abdellah Babahabib, Mohamed Elmarjany, Hicham Bakkali, Mehdi Elhassani, Jaouad Kouach, Rhali Driss Moussaoui, Mohamed Dehayni. Carcinosarcoma of the Ovary: A Case Report. *Clinical Medicine Research*. 2014;3(4):90-93.
33. Jin Z, Ogata S, Tamura G, Katayama Y, Fukase M, Yajima M, Motoyama T. Carcinosarcomas (malignant mullerian mixed tumors) of the uterus and ovary: a genetic study with special reference to histogenesis. *Int J Gynecol Pathol* 2003; 22:368-73.
34. Saito A, Kuwatsuru R, Ogishima D, et al. MR images of ovarian carcinosarcoma. *Radiat Med* 1999;17:447–450
35. Sutton GP, Blessing JA, Rosenshein N, Photopulos G, DiSaia PJ. Phase II trial of ifosfamide and mesna in mixed mesodermal tumors of the uterus (a gynecologic oncology group study). *The American Journal of Obstetrics and Gynecology*, 1989;161(2):309–312.
36. Thigpen JT, Blessing JA, Beecham J, Homesley H, Yordan E. Phase II trial of cisplatin as first-line chemotherapy in patients with advanced or recurrent uterine sarcomas: a gynaecologic oncology group study. *Journal of Clinical Oncology*, 1991;9(11):1962–1966.
37. Gershenson DM, Kavanagh JJ, Copeland LJ. Cisplatin therapy for disseminated mixed mesodermal sarcoma of the uterus. *Journal of Clinical Oncology*, 1987;5(4):618–621.
38. Thigpen JT, Blessing JA, DeGeest K, Look KY, Homesley HD. Cisplatin as initial chemotherapy in ovarian carcinosarcomas: a gynecologic oncology group study. *Gynecologic Oncology*, 2004;93(2):336–339.
39. Cicin I, Saip P, Eralp Y et al. Ovarian carcinosarcomas: clinicopathological prognostic factors and evaluation of chemotherapy regimens containing platinum. *Gynecologic Oncology*, 2008;108(1):136–140.
40. Rutledge TL, Gold MA, McMeekin DS, Huh WK, Powell MA, Lewin SN, Mutch DG, et al. Carcinosarcoma of the ovary-a case series. *Gynecol Oncol* 2006;100(1):128-132.
41. Leiser AL, Chi DS, Ishill NM, Tew WP. Carcinosarcoma of the ovary treated with platinum and taxane: the memorial Sloan-Kettering cancer center experience. *Gynecologic Oncology*, 2007;105(3):657–661.

42. Chang JS, Bristow RE, Ryu HS. Impact of complete cytoreduction leaving no gross residual disease associated with radical cytoreductive surgical procedures on survival in advanced ovarian cancer. *Annals of Surgical Oncology*, 2012;19(13):4059–4067.
43. Thigpen JT, Blessing JA, DeGeest K, Look KY, Homesley HD. Cisplatin as initial chemotherapy in ovarian carcinosarcomas: a Gynecologic Oncology Group study. *Gynecol Oncol* 2004;93(2):336-339.
44. Silasi DA, Illuzzi JL, Kelly MG, Rutherford TJ, Mor G, Azodi M, et al. Carcinosarcoma of the ovary. *Int J Gynecol Cancer*. 2008; 18(1):22–9.
45. Rutledge TL, Gold MA, McMeekin DS, Huh WK, Powell MA, Lewin SN, et al. Carcinosarcoma of the ovary-a case series. *Gynecol Oncol*. 2006; 100(1):128–32.
46. Crotzer DR, Wolf JK, Gano JB, Gershenson DM, Levenback C. A pilot study of cisplatin, ifosfamide and mesna in the treatment of malignant mixed mesodermal tumors of the ovary. *Gynecol Oncol* 2007;105(2):399-403.
47. Duska LR, Garrett A, Eltabbakh GH, Oliva E, Penson R, Fuller AF. Paclitaxel and platinum chemotherapy for malignant mixed mullerian tumors of the ovary. *Gynecol Oncol* 2002;85(3):459-463.
48. Paulsson G, Andersson S, Sorbe B. A population-based series of ovarian carcinosarcomas with long-term follow-up. *Anticancer Research*, 2013;33(3):1003–1008.
49. Rauh-Hain JA, Shoni M, Schorge JO, Goodman A, Horowitz NS, et al. Prognostic determinants in patients with uterine and ovarian carcinosarcoma. *J Reprod Med* 2013;58: 297-304.
50. Barnholtz-Sloan JS, Morris R, Malone JM Jr, Munkarah AR Survival of women diagnosed with malignant, mixed mullerian tumors of the ovary (OMMMT). *Gynecol Oncol* 2004;93(2): 506-512.
51. Rauh-Hain JA, Diver EJ, Clemmer JT, Bradford LS, Clark RM, et al. Carcinosarcoma of the ovary compared to papillary serous ovarian carcinoma: a SEER analysis. *Gynecol Oncol* 2013;131: 46-51.
52. Muller M, Dupre PF, Lucas B, Simon H, Malhaire JP, Guillemet C, Dessogne P and Pradier O: Carcinosarcoma of the ovary. *J Gynecol Obstet Biol Reprod* 2007;36: 399-402.
53. Mok JE, Kim YM, Jung MH, et al. Malignant mixed mullerian tumors of the ovary: experience with surgical cytoreduction and combination chemotherapy. *Cancer*, 1995;76(7):1209–1213.
54. Jernigan AM, Fader AN, Nutter B, Rose P, Tseng JH, Escobar PF. Ovarian Carcinosarcoma: Effects of Cytoreductive Status and Platinum-Based Chemotherapy on Survival. *Obstet Gynecol Int*, 2013;2013: 490508.
55. Morrow CP, D’Ablaing G, Brady L, Blessing J, Hreshchyshyn MM. A clinical and pathologic study of 30 cases of malignant mixed mullerian epithelial and mesenchymal ovarian tumors: A gynecologic oncology group study. *Gynecol Oncol* 1984;18: 278-292.
56. Omura GA, Brady MF, Homesley HD, et al. Long-term follow-up and prognostic factor analysis in advanced ovarian carcinoma: the gynecologic oncology group experience. *Journal of Clinical Oncology*, 1991;9(7)1138–1150.
57. Belbaraka R, Taleb A, Errihani H. A Rare Tumor of the Ovary: Carcinosarcoma. *J Med Cases* 2010;1(2):55-57.

- 385 58. Calame JJ, Schaberg A. Solid teratomas and mixed mullerian tumours of the ovary: a
386 clinical, histological and immunocytochemical comparative study. Gynaecol Oncol
387 1989;33: 212 221.
388
389